REMARKS

Reconsideration of this application and reexamination of the pending claims in view of the amendments and remarks provided herein are respectfully requested. With entry of this amendment, claims 27-36 are cancelled without prejudice to, or disclaimer of, the subject matter recited therein. Claims 37-51 are added.

New claims 37-51 find support throughout the written description of the specification as filed, such as at the locations indicated in the following table.

Claim	Support
37	Page 3, lines 19-20; page 4, lines 11-20; page 20, lines 4-7; Table 1.
38	Page 20, line 9 to page 21.
39	Page 5, line 28 to page 6, line 11.
40	Examples 1-6 at pages 8-21.
41	Page 3, lines 19-20; page 4, lines 11-20; page 20, lines 4-7; Table 1.
42	Page 20, line 9 to page 21.
43	Page 5, line 28 to page 6, line 11.
44	Examples 1-6 at pages 8-21.
45	Examples 1-6 at pages 8-21.
46	Page 3, lines 19-20; page 4, lines 11-20; page 20, lines 4-7; Table 1.
47	Page 5, line 28 to page 6, line 11.
48	Examples 1-6 at pages 8-21.
49	Original claim 12; page 3, line 28 to page 4, line 1; page 8, lines 13-17.

Claim	Support
50	Original claim 12; page 3, line 28 to page 4, line 1; page 8, lines 13-17.
51	Original claim 12; page 3, line 28 to page 4, line 1; page 8, lines 13-17.

I. Request for Rejoinder

In a Restriction Requirement included in Paper No. 8, the Office required restriction between Groups I-V, on the basis that these groups of claims allegedly did not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they allegedly lacked the same of corresponding special technical features. (Paper No. 8 at page 2.) In response, Applicants elected to prosecute the claims of Group I, allegedly drawn to a non-human α-tocopherol knockout animal.

New claims 37-48 correspond to elected Group I. Applicants are also adding claims 49-51, which correspond to Group III, claim 25, allegedly drawn to a method of screening medicaments *in vivo* using a transgenic non-human mammal. Applicants submit that unity of invention exists between claims 49-51, and claims 37-48, under PCT Rules 13.1 and 13.2. Applicants respectfully request rejoinder of claims 49-51 to claims 37-48 no later than issuance of a Notice of Allowance in this application.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

The Office maintained the rejection of claims 27-36 under 35 U.S.C. § 112, first paragraph, alleging that "the specification, while being enabling for a homozygous transgenic mouse whose genome comprises a homozygous disruption of the

endogenous α-TTP gene wherein the mouse exhibits non-detectable levels of vitamin E or wherein the mouse, when female, exhibits a failure to maintain pregnancy, does not reasonably provide enablement for all other mice embraced by the claims." (Office Action at page 2.) Applicants have cancelled claims 27-36 herein, rendering this rejection moot. Applicants also respectfully submit that the rejection should not be applied to the new claims.

New claims 37-40 and 49 recite "[a] transgenic mouse whose genome comprises a homozygous disruption of the endogenous α-TTP gene." The claims also recite a phenotype of these homozygous mice; namely, "wherein α-TTP expression is inhibited such that the transgenic mouse does not exhibit detectable plasma levels of α-tocopherol." Applicants submit that claims 37-40 and 49 are enabled and that this ground of rejection should not be applied to them.

New claims 46-48 and 51 recite "[a] transgenic mouse whose genome comprises a heterozygous disruption of the endogenous α-TTP gene." The claims also recite a phenotype of these heterozygous mice; namely, "wherein α-TTP expression from the disrupted α-TTP allele is inhibited such that the transgenic mouse exhibits about one-half the plasma level of α-tocopherol of a corresponding mouse that does not comprise a disrupted endogenous α-TTP gene when the mice are fed with a diet comprising the same amount of α-tocopherol." Applicants submit that the specification enables one of skill in the art to make the claimed heterozygous mice. The specification also discloses that such mice are useful for, among other things, screening for therapeutic and prophylactic agents for treatment of diseases caused by impairment of

α-TTP. Applicants submit that claims 46-48 and 51 are enabled and that this ground of rejection should not be applied to them.

Finally, new claims 41-45 and 50 recite "[a] transgenic mouse comprising a disrupted endogenous α-TTP gene." The claims further recite that "α-TTP expression from the disrupted α-TTP allele is inhibited such that transgenic mice homozygous for the disrupted allele exhibit a vitamin E deficiency phenotype." In rejecting claims 27-36, the Office stated that the specification does not enable one of skill in the art to use heterozygous mice, because the specification fails to teach that "transgenic mice comprising a heterozygous disruption of the α-TTP gene . . . have a phenotype so as to provide a use for the mouse." (Office Action at page 3.) According to the Office, the rejected claims "encompass chimeric and heterozygous mice exhibiting any phenotype, including a wild-type phenotype." (Office Action at page 3.) The Office further states that "[t]he specification does not teach how to use the claimed mice exhibiting a wild-type phenotype." (Office Action at page 3.) Applicants traverse this ground of rejection to the extent that the Office may seek to apply it to new claims 41-45 and 50.

Applicants maintain that the Office's characterization of the specification and the claimed mice is not correct. Specifically, as Applicants stated in their previous response, the specification teaches that a transgenic mouse whose genome comprises a heterozygous disruption of the endogenous α-TTP gene is useful, for example, to make a transgenic mouse whose genome comprises a homozygous disruption of the endogenous α-TTP gene. Indeed, such mice were "used" to make the homozygous mice of the invention. *See, e.g.*, Example 4 at pages 17-18.

The Office acknowledges that Applicants' claimed heterozygous mice may be used as intermediates to make Applicants' claimed homozygous mice. The Office also acknowledges that it is well established by precedent, such as *Reiners v. Mehltretter*, 236 F.2d 418, 422 (C.C.P.A. 1956), that an intermediate that can be used to make a final product that is itself directly useful satisfies the utility and enablement requirements of 35 U.S.C. §§ 101, 112. The Office also does not contend that the homozygous mice that can be made with the claimed heterozygous mice are not directly useful. In fact, the Office apparently acknowledges that these mice are enabled for a disclosed utility.

However, the Office distinguishes this precedent, derived from cases addressing chemical intermediates, from Applicants' claims, stating that

> The chimeric and heterozygous mice encompassed by the claims are not well-defined and, as claimed, can include mice exhibiting any phenotype, including wildtype. The well-defined chemical intermediates of *Reiners v. Mehltretter* do not apply to the heterozygous and chimeric mice of the instant invention as broadly claimed. Therefore, specification does not enable one of skill in the art to use the chimeric and heterozygous mice encompassed by the claims.

(Office Action at pages 3-4.) Applicants note that the Office has not cited any precedent to support its novel differential treatment of mice and chemical intermediates with respect to the utility requirement.[1]

Instead, the Office bases its conclusion that differential treatment is appropriate, on its contention that a transgenic mouse whose genome comprises a heterozygous disruption of the endogenous α-TTP gene may have a phenotype that is not taught by Applicants. Applicants submit that this point is not relevant to the issue of enablement of Applicants' claims. Based on Applicants' disclosure and the knowledge which one of skill possesses, the genus of transgenic mice whose genome comprises a heterozygous disruption of the endogenous α-TTP gene is fully enabled to be used to make a transgenic mouse whose genome comprises a homozygous disruption of the endogenous α-TTP gene. This is so regardless of whether such mice may exhibit a phenotype contemplated by the Office. Thus, the full scope of Applicants' claims is enabled for a disclosed utility, and claims 41-45 and 50 satisfy the utility and enablement requirements of 35 U.S.C. §§ 101 and 112.

The Office further supported the enablement rejection by stating that "the specification fails to provide the guidance necessary to generate a genetically modified

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[1] Indeed, this distinction does not appear to be generally followed by the Office, because claims to heterozygous mice that do not themselves exhibit any phenotype were allowed in at lease three patents issued in 2003 and 2004. For example, claim 13 of U.S. Pat. No. 6,605,753 B1, claim 1 of U.S. Pat. No. 6,730,821 B2, and claim 3 of U.S. Pat. No. 6,784,335 B2, all of which are attached hereto for the Office's convenience, are directed to a heterozygous mouse and do not require that the heterozygous mouse exhibit a phenotype. Rather, each of these claims defines the allele of the claimed heterozygous mouse by reciting a phenotype exhibited by a mouse that is homozygous for the allele. In this regard these patented claims are similar to Applicants' claims 41-45 and 50. Applicants submit that these allowed claims demonstrate that the Office's current rejection of Applicants' claims relies on an interpretation of the requirements of 35 U.S.C. §§ 101 and 112 that is neither compelled by the statute nor by case law, and that is not even generally followed by the Office.

mouse comprising a disruption in the α-TTP gene wherein the mouse exhibits any vitamin E deficiency phenotype other than non-detectable levels of vitamin E and failure of female mice to maintain pregnancy." (Office Action at page 4.) Applicants note that the new claims recite "wherein α-TTP expression is inhibited such that the transgenic mouse does not exhibit detectable plasma levels of α-tocopherol" or "wherein the mouse is a pregnant female, and wherein the pregnant female fails to maintain pregnancy as assayed by the fetal resorption-gestation test." Thus, Applicants submit that this basis for the enablement rejection does not apply to the new claims.

The Office further supported the enablement rejection by stating that "[d]ue to the lack of guidance provided by the specification with respect to how to genetically modify the α-TTP gene in a mouse using any means other than transgene insertion into the endogenous α-TTP gene, it would require undue experimentation to generate the genetically modified mice that are broadly encompassed by the claims." (Office Action at page 5.) The Examiner suggested that replacing the phrase "genetically modified" with "transgenic" in claims 27-36 and correlating a disruption of the α-TTP gene to the transgene would overcome this rejection. Applicants thank the Examiner for this suggestion and have adopted it in the new claims. Thus, Applicants submit that this basis for the enablement rejection does not apply to the new claims.

The Office further supported the enablement rejection, stating that "[i]t would require undue experimentation for one of skill in the art at the time of filing to generate a transgenic mouse whose genome comprises a transgene comprising a knockout allele of the α-TTP gene wherein the knockout allele does not affect the endogenous α-TTP gene and wherein the mouse exhibits a vitamin E deficiency." (Office Action at page 5.)

The Examiner suggested that Applicants insert the term "endogenous" into the claims to overcome this rejection. Applicants thank the Examiner for this suggestion and have adopted it in the new claims. Thus, Applicants submit that this basis for the enablement rejection does not apply to the new claims.

The Office further supported the enablement rejection by stating that "[c]laims 27-36 encompass mice comprising a knockout allele of the α-TTP gene wherein expression from the knockout allele is partially inhibited. The specification defines "inhibited" as encompassing both complete and partial inhibition (page 4, paragraph 2). The specification is not enabling for partially inhibiting expression of the α-TTP gene." (Office Action at page 6.) Applicants note that the new claims do not include the term "knockout". Thus, Applicants submit that this basis for the enablement rejection does not apply to the new claims.

Applicants submit that the new claims are fully enabled by the specification in view of the knowledge of the skilled artisan as of the effective filing date of this application. Accordingly, Applicants respectfully submit that the enablement rejection should not be applied to the new claims.

III. Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office maintained the rejection of claims 27-36 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (Office Action at pages 7-8.) Applicants have cancelled claims 27-36 herein, rendering this

rejection moot. Applicants also respectfully submit that the rejection should not be applied to the new claims.

In support of this rejection, the Office stated that "[t]he term 'knockout allele' in claims 27-36 is used [ ] to mean 'hypomorphic allele' or 'allele with reduced expression', while the accepted meaning is 'null allele.' The term is indefinite because the specification does not clearly redefine the term." Applicants note that the new claims do not include the term "knockout allele." Applicants submit that the new claims are definite and in compliance with 35 U.S.C. § 112, second paragraph. Applicants respectfully submit that this rejection should not be applied to the new claims.

III. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims 37-51.

If this paper does not result in the issuance of a Notice of Allowance, Applicants respectfully request that the Examiner contact the undersigned at 650-849-6607.

Please grant any extensions of time required to enter this response and charge

any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: October 6, 2004

By: Jean Burke Fordis
Jean Burke Fordis
Reg. No. 32,984

Attachments: U.S. Pat. No. 6,605,753 B1
U.S. Pat. No. 6,730,821 B2
U.S. Pat. No. 6,784,335 B2